УДК 616.441-008.63

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CONGENITAL HYPOTHYROIDISM (REVIEW)

Congenital hypothyroidism (CH) is one of the most common preventable causes of mental retardation in children, with an incidence of approximately 1:2800 newborns. Early diagnosis and treatment prevent the destructive outcome of mental retardation. Clinical features of CH are subtle and are not evident early in the neonatal period. In this regard, newborn screening for CH is carried out in all developed countries of the world. Therefore, universal newborn screening (NS) is effective in detecting CH and realizing early treatment. This article reviews the current literature regarding the epidemiology, etiology, classification, clinical features, diagnosis of CH, treatment and prognosis of CH and outlines the importance of universal newborn screening in preventing mental retardation. We performed a literature review using the PubMed database. Results focused on reviews and articles published from 2013 through 2018.
Keywords: *Congenital hypothyroidism, newborn screening, thyroid stimulating hormone, dyshormonogenesis, dysgenesis*

Introduction.
Congenital hypothyroidism is the most common preventable cause of mental retardation. Thyroid hormones play a crucial role in the early development of the nervous system, so that untreated severe CH results in neurological and psychiatric deficits, including intellectual disability, spasticity, and contraventions of gait and coordination. Screening programs, which have been in operation over the last 30 years in most industrialized countries, have led to the successful early detection and treatment of infants with CH and have eliminated the severe neurodevelopmental deficits resulting from late diagnosis. Studies on cognitive function in patients with CH treated soon after birth have shown that normal development can be achieved in most patients.

Epidemiology.
Over the last several years, reports from newborn screening programs around the world have described an increase in the incidence of congenital hypothyroidism. Based on article of Ari J.Wassner and Rosalind S. Brown: Congenital hypothyroidism: recent advances, the incidence of congenital hypothyroidism compared with the rate of 1:3000–1:4000 when screening was introduced have increased rates ranging from 1:1400 to 1:2800, which have been reported recently by screening programs in many countries including the USA, Canada. [2]The increasing incidence of CH has also been documented in European populations and presently is as follows: British, 1in 1,077; Greeks, 1 in 1,749; and Italians, 1 in 2,200. There is a 2:1 female to male ratio in CH. [3]Based on data from recent articles factor contributing to this change may be the widespread lowering of thyroid-stimulating hormone (TSH) screening cutoffs that leads to detection of milder cases. In a comprehensive review of newborn screening strategies for congenital hypothyroidism around the world, Ford and LaFranchi found that lowering the TSH cut-offfrom greater than 20–25mIU/l to greater than 6–10mIU/l in six national newborn screening programs resulted in a 2.2-fold increase in the average incidence of congenital hypothyroidism (from 1:3264 to 1:1464). [1,2]The risk of CH is higher among newborns with birth weights less than 2,000 g and greater than 4,500 g. Transient CHis more common among premature infants. [3, 4]

Etiology and Classification.
Eighty five percent of cases of primary permanent CH are due to abnormal thyroid gland formation (thyroid dysgenesis). About two-thirds of the cases of thyroid dysgenesis are due to ectopic thyroid tissue, the remaining cases are due to aplasia or hypoplasia. Defects in PAX8 (paired domain homeobox), TTF-1 и TTF-2 (thyroid transcription factors 1 and 2) are found in 2–5% of cases of thyroid dysgenesis. [5]A defect in the normal production of thyroid hormones due to defects in enzymes and ion transporters, known as dyshormonogenesis, corresponds to approximately 10% to 15% of the cases of CH. These conditions are inherited in an autosomal recessive pattern. Dyshormonogenesis is caused by defects of thyroid hormone synthesis: mutations of thyroglobulin (TG), thyroid peroxidase (TPO), dual oxidase 2 (DUOX2), the sodium-iodide symporter (SLC5A5)the TSH receptor.[6, 7]
CH can be classified into transient and permanent. In transient CH, euthyroid status returns after few weeks to months of life, while in permanent CH, the deficiency ofthyroid hormone is life-long. Transient CH can be due to one of the following reasons:
1. Deficiency or excess of iodine in the mother;
2. Transplacental transfer of TSH-receptor blocking antibodies from mothers with autoimmune thyroid disease including Hashimoto thyroiditis and Graves' disease.
3. Exposure to high doses of iodine during fetal or early neonatal life.
4. Maternal use of anti-thyroid drugs that can cross the placenta.
5. Heterozygous mutations of THOX2 or DUOXA2. Children with large congenital hepatic hemangiomas due to increased type 3 deiodinaseactivity may also have transient CH.[6]
CH can also be classified as primary and secondary. In primary CH, there is primary deficiency of thyroid hormone either due to dysgenesis or dyshormonogenesis. While in secondary CH (also called Central CH) there is isolated TSH deficiency and combined deficiency of pituitary hormones (hypopituitarism).

Clinical features.
Most newborns with CH do not have obvious clinical manifestations at birth due to the transplacental passage of maternal thyroid hormones. The most typical signs of the disease in the early postnatal period and clinical features that appear after the neonatal period are presented in the Table 1.[6]

Table 1 - Signs and Symptoms of Congenital Hypothyroidism [6].

Early findings	Late findings (after the neonatal period)
Macrosomia	Poor sucking effort
Decreased activity	Developmental delay
Largeanteriorfontanelle	Decreasedactivityandlethargy
Edema of the eyelids, hands, and feet	Poorgrowth
Prolongedjaundice	Umbilicalhernia
Hypotonia	Mottled, cool, and dry skin
Coarsefacialfeatures	Difficultbreathing
Hypothermia	Macroglossia
Pallor	Generalizedswelling (myxedema)
Goiter	Hoarsecry
Protuberantabdomen	

CH can also be a part of a congenital syndrome. The most commonly reported syndrome is Pendred syndrome, which is inherited as autosomal recessive and characterized by sensorineural deafness and a defect of organification of Iodide, Alagille syndrome (JAG1); and neonatal diabetes, congenital glaucoma, and liver and kidney abnormalities (GLIS3).

Diagnosis of Congenital Hypothyroidism

Newborn screening. The first program for newborn screening for CH was started in Canada in 1973. Today screening for CH is in operation in most parts of the world. Early detection and treatment of CH through neonatal screening prevents neurodevelopmental disability and optimizes developmental outcomes. Currently majority is using initial TSH measurementand some are measuring FT4 and TSH simultaneously. Almost everywhere dried blood samples (DBS) specimens are generally used. There are exceptions where cord blood specimens are used instead of DBS (generally very small jurisdictions where births occur at few or only a single location). [8]Newborn thyroid screening samples are collected from a heel-prick blood specimen on a filter paper between the second and fifth days after birth, to minimize the false positive high TSH values because at delivery, exposure to a cold environment causes a surge of thyrotropin within 30 minutes, as high as 160 mIU/L, with a subsequent increase in T4 and total triiodothyronine (T3). Thyrotropin decreases significantly by 48 hours after birth, reaching infant levels of less than 10 mIU/L by the fifth day after birth. [6]The filter paper is mailed to a centralized laboratory.Some programs obtain a second sample between the second and sixth weeks of age or upon hospital discharge if the infant has been admitted to a neonatal intensive care unit. Some newborns who are discharged from the hospital on the first day after birth have the sample taken at this time. The European Society for Pediatric endocrinology (ESPE) guidelines advised repeat screening in preterm neonates with gestational age less 37 weeks, low birth weight and very low birth weight neonates, ill neonates admitted to the Neonatal Intensive Care Unit, multiple births, and in babies whom sample is collected in first 24 h. [9, 16]

Any abnormal result on newborn screening should prompt immediate confirmation (ideally within 24 hours) by measuring serum concentrations of TSH and FT4. It is important to be aware that some laboratories may report TSH and FT4 reference ranges that are not applicable to infants, so all results should be interpreted based on gestational age and postnatal age-specific reference ranges (Table 2).

Table 2.Standards of TSH level in children [10]

Age	TSH,mIU / l
newborns	1,3-19
10 weeks	0,6-10
14 months	0,4-7,0
5 yearsold	0,4-6,0
14 years old	0,4-5,0

Infants in whom the TSH is elevated on newborn screening have primary hypothyroidism. If the newborn screening TSH is greater than 40 mIU/L, severe hypothyroidism should be presumed and treatment should be initiated as soon as confirmatory serum laboratory tests are drawn, without waiting for the results. Once confirmatory measurements are available, treatment should be initiated in any patient with a serum TSH of greater than 20 mIU/L, or with a low FT4 concentration regardless of TSH concentration.

Infants with a slight elevation of TSH and normal FT4 levels have mild hypothyroidism, and current data are indeterminate as to the neurodevelopmental risks posed by this degree of hypothyroidism and whether treatment is of benefit. A series of recent studies of Belgian children showed no association between mild TSH elevation on newborn screening and cognitive or psychomotor development at preschool age. In contrast, a population-based study of more than 500,000 Australian children demonstrated a positive association between increasing newborn screening TSH concentrations of up to 12 to 14 mIU/L, and an increased risk of adverse developmental or educational outcomes. Both studies have limitations, however, and the true risk posed by mild congenital hypothyroidism remains unclear. For patients with confirmatory serum TSH levels of 6 to 20 mIU/L and normal FT4 levels, it is reasonable to follow serum thyroid function tests closely (every 1–2 weeks) and to initiate treatment if TSH is increasing or if FT4 decreases to below normal. [11, 12, 13]

The European Society for Pediatric endocrinology (ESPE) guidelines (2014) have given following advice:

TSH ≥ 40 mU/l of whole blood on DBS, start treatment immediately.

TSH < 40 mU/l of whole blood treatment can be postponed for 1-2 days to get venous sample result.

TSH > 20 mU/l in venous sample requires treatment, irrespective of FT4 levels

Low serum FT4 regardless of TSH level should be treated immediately.

If venous TSH concentration is ≥6 to 20 mU/l beyond 21 days in a well baby with a FT4 concentration within the limits for age, they suggest investigation, which should include diagnostic imaging, to try to obtain a definitive diagnosis. [9]

The goal of screening for CH should be to detect all forms of primary CH – mild, moderate and severe, with particular efforts to detect those patients with severe CH, where morbidity is high if the disease is not detected and treated until several months after birth.

Further imaging and laboratory evaluation may be performed to clarify the origin of thyroid disorder. The presence or absence of a normally located thyroid gland can be assessed by ultrasound or thyroid scintigraphy (using 99mTc or 123I), which can help distinguish between thyroid dysgenesis and dyshormonogenesis. While hypothyroidism due to dysgenesis is usually permanent, about 35% of patients with aneutopic thyroid gland have transient disease and will not require lifelong therapy. The potential presence of TSH receptor-blocking antibodies should be considered in patients with aneutopic thyroid gland on ultrasound even if there is no maternal history of autoimmune thyroid disease. If TSH receptor antibodies are documented in maternal or neonatal serum, they portend a transient course of hypothyroidism that resolves within 3–4 months, although neurodevelopment may be impaired if the mother had unrecognized hypothyroidism during gestation, even with institution of prompt postnatal treatment.

Central or Secondary/Tertiary Hypothyroidism.

Central hypothyroidism is caused by insufficient thyrotropin stimulation of a normal thyroid gland due to a disorder of the hypothalamus or pituitary gland. The prevalence of central hypothyroidism does not differ by sex. The most common causes of central hypothyroidism are combined pituitary hormone deficiencies, which may be genetic or secondary to hypothalamic and/or pituitary neoplasias or trauma. Isolated central hypothyroidism is rare. The diagnosis is made when FT4 levels are low and thyrotropin levels are normal, low, or slightly elevated. Therefore, clinicians or newborn screening programs that only evaluate thyrotropin levels may miss the diagnosis of central hypothyroidism.

Treatment of congenital hypothyroidism.

Detection by newborn screening and optimal management has essentially eliminated the mental retardation associated with untreated CH. The principles of optimal management include early onset of treatment, a starting dose of levothyroxine (L-T4) tailored to the severity of hypothyroidism, to rapidly normalize serum T4 and TSH, and appropriate frequency of monitoring thyroid function. The treatment should be commenced immediately after confirmation of diagnosis based on NS. Initiation of treatment within first 2 weeks of life is crucial for the normal neurodevelopment. Levothyroxine (L-T4) is the only recommended treatment for replacement therapy. Most T3 in the brain is formed from local deiodination of T4; thus, the addition of T3 replacement is not necessary for normal neurodevelopment. The initial L-T4 dose recommended by both the American Academy of Pediatrics and the European Society for Pediatric Endocrinology is 10–15 mg/kg/day (Table 3). [9, 10]Rapid normalization of thyroid function has been demonstrated to be important in achieving optimal neurodevelopmental outcome. This can best be accomplished by tailoring the initial L-T4 dose within the 10–15 mg/kg/day range to the severity of hypothyroidism.

Table 3 - Replacement dosing of levothyroxine (LT4) in congenital hypothyroidism [9, 10]

Age	LT4 dose (mcg/kg/day)
0–3 months	10–15
3–12 months	6–10
1–3 years	4–6
3–10 years	3–5
10–16 years	2–4
>16 years	1.6

The L-T4 is available in tablet form in worldwide and is recommended to be used in tablet form by crushing and mixing in few milliliters if water or breast milk immediately before administration. The L-T4 is available in liquid form in Europe which is produced pharmaceutically and licensed for use. This liquid form is reliable in dosing and convenient for infants. [14]

The goal of treatment is to achieve euthyroidism rapidly and to maintain it as consistentlyas possible thereafter. Normalization of serum TSH and FT4 levels within 2 weeks after starting therapy seems to improve cognitive outcomes, and under treatment in the first years of life is associated with adverse neurodevelopmental outcomes. However, it is also important to avoid overtreatment with LT4, which may also be harmful.[15] Because the currently recommended starting dose of LT4 often leads to overtreatment, careful surveillance—and often LT4 dose reduction—is necessary after initiating treatment to normalize thyroid function quickly without over treating.

Monitoring.

Control studies of levels of THS and FT4 should be conducted in the first year of life every 2-3 months, after a year every 3-4 months. During the first 6 weeks from the beginning of replacement therapy, only FT4-level control studies are conducted every 2 weeks. It is advisable to start the control determination of the levels of THS and FT4 simultaneously not earlier than 6 weeks from the start of treatment. Orientation in children of the first year of life only at the level of TSH because of a possible violation of its regulation on the principle of feedback can lead to the appointment of unnecessarily high doses of levothyroxine. In cases of normal levels of FT4 (individually for each laboratory), the dose of levothyroxine may be considered adequate.

Prognosis.

In general, developmental outcomes in congenital hypothyroidism are excellent, and early and adequate treatment with LT4 prevents severe neurocognitive deficits and results in normal global intelligence (IQ). However, mild deficits in several domains—including motor development, verbal skills, attention, and memory—may occur in some patients despite optimal postnatal treatment, particularly those born with very low serum concentrations of FT4.[17]

Conclusion.

Congenital hypothyroidism is common and can cause severe neurodevelopmental morbidity. Prompt diagnosis and the institution of early and adequate treatment are

critical to preventing these adverse effects and optimizing long-term outcomes. Universal newborn screening is an important tool for the detection of congenital hypothyroidism and has led to a dramatic reduction in severe intellectual disability owing to this condition. Treatment with LT4 should be initiated as early as possible, ideally within the first 2 weeks of life, and normal thyroid function should be achieved rapidly and maintained carefully. When properly managed, patients with congenital hypothyroidism overall have an excellent prognosis, but subtle deficits may remain in patients with the most severe hypothyroidism.

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ТУА БІТКЕН ГИПОТИРЕОЗ (ӘДЕБИ ШОЛУ)

Түйін: Туа біткен гипотиреоз - бұл балалардың ақыл-ойы артта қалуының ең жиі кездесетін себептерінің бірі, шамамен 1: 2800 жаңа туылған сәби. Ерте диагноз қою және емдеу ақыл-ойдың артта қалуының бұзылуына жол бермейді. Туа біткен гипотиреоздің клиникалық ерекшеліктері аса көрінбейді және жаңа туған кезеңде ерте анықталмайды. Осыған орай, туа біткен гипотиреозды анықтау мақсатында жаңа туған нәресте скринингі әлемнің барлық дамыған елдерінде жүргізіледі. Осылайша, неонатальды скрининг туа біткен гипотиреозды дер кезінде диагностикалауда және емдеуде тиімді. Бұл мақалада эпидемиология, этиология, жіктеу, клиникалық ерекшеліктері, туа біткен гипотиреозды диагностикалау, емдеу, болжау туралы қорытынды жасалып, ақыл-ойдың артта қалуында жаңа туған нәрестелердің неонатальді скринингінің маңызы баяндалады. PubMed дерекқорын пайдаланып, әдеби шолу жасадық. Ақпарат 2013 және 2018 жылдар аралығындағы жарияланымдар мен мақалаларға бағытталған.
Түйінді сөздер: Туа біткен гипотиреоз, неонатальды скрининг, тиреотропты гормон, дисгормоногенез, дисгенез

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ВРОЖДЕННЫЙ ГИПОТИРЕОЗ (ОБЗОР ЛИТЕРАТУРЫ)

Резюме: Врожденный гипотиреоз (ВГ) является одной из наиболее распространенных причин умственной отсталости (кретинизма) у детей, встречающийся с частотой приблизительно 1: 2800 новорожденных. Своевременная диагностика и лечение предотвращают необратимые негативные последствия умственной отсталости. Клиническаякартина ВГмалозаметна и не проявляется в раннем неонатальном периоде. В связи с этимво всех развитых странах мира проводится массовое обследование на ВГ. Таким образом, неонатальный скрининг эффективен в своевременной диагностике и лечении ВГ. В нашем обзоре обобщены эпидемиология, этиология, классификация, клинические особенности, диагностика ВГ, лечение, прогноз и излагается важность универсального скрининга новорожденных в профилактике умственной отсталости. Мы провели обзор литературы с использованием базы данных PubMed. Сведения были сосредоточены на обзорах и статьях, опубликованных с 2013 по 2018 год.
Ключевые слова: Врожденный гипотиреоз, неонатальный скрининг, тиреотропный гормон, дисгормоногенез, дисгенезия